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Cell membrane-coated nanoparticles for cancer therapy

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ABSTRACT

Despite the advantages of nanoscale drug delivery systems, traditional nanoparticles often encounter challenges such as detection and elimination by the immune system. To circumvent these limitations, scientists have created biomimetic nanoparticles that extend circulation time, decrease clearance rates, and optimize drug delivery. The integration of cell membranes onto nanoparticle surfaces yields Cell Membrane-coated Nanoparticles (CMNPs) that exhibit behavior akin to actual cells while offering superior structural robustness and stability. A variety of cell membranes, including those of red blood cells, white blood cells, and cancer cells, lend unique properties and targeting capabilities to CMNPs. This review outlines the diagnostic and therapeutic roles of CMNP-based drug delivery systems in oncology and contemplates their possible clinical impact.

KEYWORDS

Cell membrane; Nanoparticles; Drug delivery; Cancer

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1. Introduction

Neoplasms pose a significant global health challenge and represent a considerable threat to human welfare. According to the World Health Organization's "Global Cancer Report 2020," neoplasms top the list of causes of mortality among individuals under 70 in the majority of countries1. Neoplastic cells are known for their uncontrolled proliferation, maintained through self-sustaining growth signals, resistance to growth inhibitors, and evasion of apoptosis2. Moreover, these cells manage to dodge immune detection, metastasize to various organs from their primary sites, and can even evolve adaptive strategies to resist effective therapies through additional genetic mutations3. The primary clinical responses to neoplasms include chemotherapy, radiotherapy, and immunotherapy, in addition to surgical intervention. Other treatments under development and exploration include photothermal therapy (PTT), photodynamic therapy (PDT), and gene therapy. However, these methods still prove suboptimal in treating neoplasms due to undesirable pharmacokinetics, poor penetration, non-targeted delivery, and harsh side effects. To address these limitations, nanoparticle-based drug delivery systems (DDS) have drawn significant research attention in the field of cancer diagnostics and therapeutics4. Nanoparticles, generally sized between 1 and 1000 nm, display excellent drug delivery characteristics, particularly those within the 10 to 100 nm range, which exhibit the highest drug delivery efficiency5. Numerous nanoparticle types, such as polymeric micelles, liposomes, and metallic nanomaterials, have been designed for neoplastic drug delivery. Among the vast range of nanomaterials, biomaterials like natural elements (e.g., chitosan, collagen, and hyaluronic acid), synthetic polymer nanomaterials, lipid-based nanocarriers, and inorganic nanomaterials, demonstrate considerable merits for drug delivery. These include superior biocompatibility and biodegradability, flexible dimensions, and substantial drug-loading capacities 6, 7 (Figure 1). These nanomaterial-based DDS can effectively deliver drugs via passive or active targeting, offering high drug-loading capacity, extended circulation times, and minimal systemic toxicity. Nanoparticles achieve passive targeting through the enhanced permeability and retention (EPR) effect, thereby enabling efficient therapeutic drug delivery. When these nanomaterials have stimuli-responsive properties or targeting ligands, DDS based on such nanomaterials can deliver drugs even more efficiently8. In conclusion, biomaterial-based nanocarrier systems offer numerous advantages in drug delivery and play a pivotal role in creating anti-neoplastic drug nanocarrier systems.

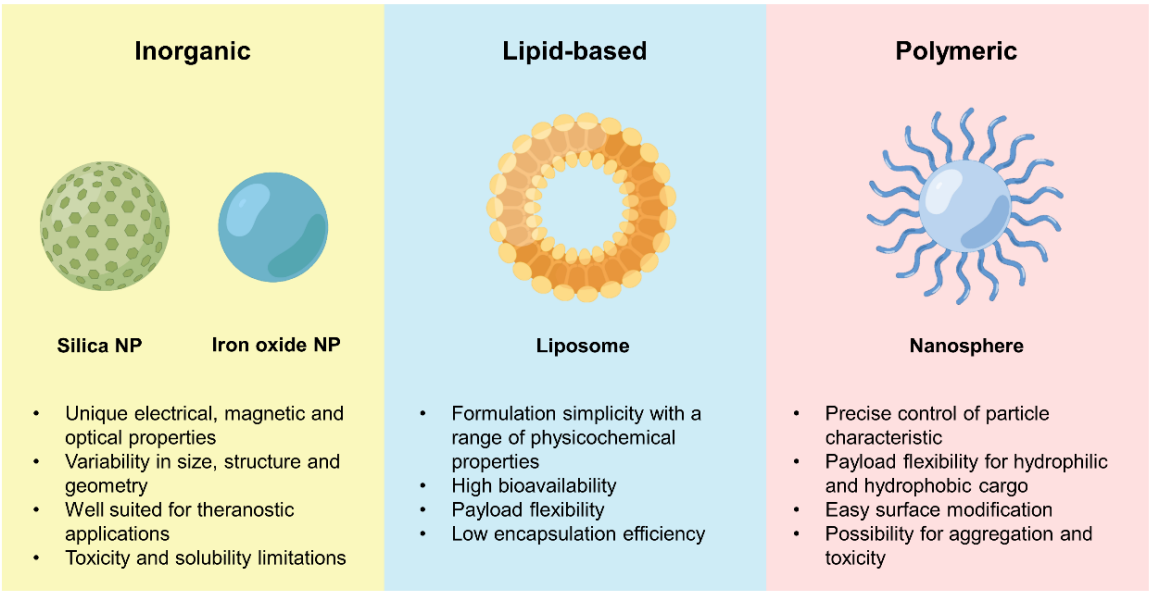

Figure 1. Common classifications and advantages/disadvantages of nanoparticles.

2. Nanocarrier systems in tumor diagnosis and treatment

Compared to traditional treatment approaches, antineoplastic drugs leveraged on nanocarrier systems demonstrate superior efficacy and fewer side effects. Additionally, nanocarriers exhibit excellent water solubility, which makes them ideal vehicles for hydrophobic drugs, thereby enhancing the bioavailability of antineoplastic drugs and reducing reliance on organic solvents. Nanomaterials can also mitigate some disadvantages associated with poor chemical stability of certain drugs. To boost the delivery efficiency of nanomaterials, nanocarrier systems can be fashioned as environmentally responsive or stimuli-responsive smart carriers, enabling controlled drug release. This key advantage dramatically diminishes premature drug release from nanocarriers prior to reaching the tumor site, reduces drug accumulation in non-tumor areas, and consequently lowers drug-related systemic toxicity. Another significant advantage of nanocarriers is their capacity to conjugate targeting moieties, thereby actively directing drugs to tumor tissues and ensuring efficient delivery of tumor imaging agents and cytotoxic drugs. Moreover, nanoparticles provide an abundance of sites for binding or adhering to specific targeting molecules, empowering them to target tumor cells, tissues, or blood vessels. Targeting molecules enhance the interaction between nanoparticles and target cells, thereby increasing the cellular uptake of nanoparticle-based drugs (Figure 2). Nanomedicines capable of imaging can be produced by integrating imaging functional units within nanocarriers. These nanomedicines can be employed for tumor diagnosis and staging, investigating pharmacokinetics, and monitoring therapeutic outcomes. Some nanomaterials inherently possess optical, thermal, electrical, or magnetic properties, making them highly effective in early tumor detection and diagnosis. Nanomaterial-based imaging probes have shown exceptional signal sensitivity and spatial resolution. In recent years, the continuous development of nanoparticles with tumor diagnostic and imaging capabilities, such as liposomes containing radioactive isotopes or fluorescent labels, radiolabeled copolymer nanoparticles, nanoparticles loaded with photoacoustic or photothermal drugs, and polymer nanoparticles carrying magnetic resonance imaging agents, has been observed. These nanomedicines have demonstrated remarkable tumor imaging capabilities in in vivo animal studies. Some nanoparticles also incorporate tumor-targeting moieties to increase tumor accumulation and enhance imaging capabilities. The premise of nanomedicine for tumor treatment is that nanomedicines can augment therapeutic effects on tumors while reducing systemic toxicity. Presently, nanocarrier systems have been utilized to deliver therapeutics to enhance tumor chemotherapy, radiotherapy, immunotherapy, PTT, PDT, and gene therapy, while minimizing side effects. When evaluating the effectiveness and side effects of nanomedicines, one should consider not only the absolute drug accumulation in tumors but also the relative increase in drug concentration compared to normal tissues. Traditional nanomedicines rely on the enhanced permeability and retention (EPR) effect to boost their therapeutic efficacy; however, the considerable heterogeneity among tumors restricts the advantages of the EPR effect in enhancing the delivery efficiency of nanomedicines. To further augment the delivery efficiency of nanomedicines, tumor-targeting nanocarrier systems based on tumor characteristics have been developed, allowing for the selection or even customization of nanocarrier systems to achieve optimal tumor targeting. These nanoparticles can also adjust the tumor microenvironment to enhance nanoparticle accumulation in tumors. For certain tumor immunotherapeutic agents, nanocarriers need to target lymphoid organs, such as lymph nodes, to optimize their accumulation in these organs, thereby enhancing the therapeutic effects of tumor immunotherapy.

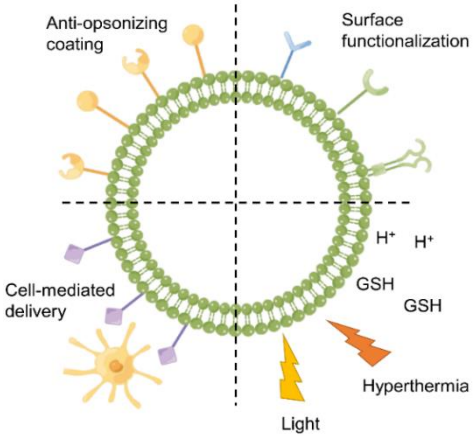

Figure 2. Design strategies for nanoparticles.

3. Classification of cell membranes-coated nanoparticles

While nanoscale drug delivery systems provide numerous benefits, the exogenous nature of nanoparticles makes them vulnerable to detection and removal by the immune system. In response, biomimetic nanoparticles have been engineered to extend circulation time, decrease clearance rates, and enhance drug delivery efficiency. PEGylation technology has been widely used to reduce the clearance of nanoparticles; however, studies suggest that repeated administration of PEGylated nanoparticles can stimulate the production of anti-PEG antibodies, paradoxically increasing their susceptibility to immune system clearance. Lipids, the primary components of cell membranes, have also been employed to fabricate biomimetic liposomes mimicking biomembranes. Nevertheless, their incomplete structure and instability restrict their utility as drug delivery systems (DDS). Recently, innovative cell membrane-coated biomimetic nanoparticles have been developed for drug delivery. Cell membranes (CM) can be draped over nanoparticle surfaces, generating CM-coated nanoparticles (CMNP) that exhibit cell-like behavior. These nanoparticles boast a robust and stable core structure capable of protecting a variety of therapeutic agents they carry. Additionally, CM can imbue CMNPs with extended circulation time, superior targeting capabilities, and other characteristics of the source cells. For example, red blood cell membranes (RBM) can be used to evade the immune system and extend the in vivo circulation time of nanomedicines; white blood cell membranes can avoid photosensitization and bypass clearance by the reticuloendothelial system, and can be leveraged for targeting inflamed sites; cancer cell membranes (CCM) can bestow homotypic targeting abilities to nanoparticles and serve as a source of tumor-associated antigens (TAAs). The upcoming section will summarize cancer diagnostic and therapeutic drugs based on CMNP nanoscale drug delivery systems and explore their potential clinical applications (Figure 3).

3.1. Red cell membranes-coated nanoparticles

Biomimetic modifications based on red blood cells represent one of the most advanced surface alterations currently studied in nanocarrier research. Red blood cells, the most numerous and long-lived blood cells in the body with a lifespan of up to 100-120 days, can navigate the cardiovascular system and normal tissues without being detected or engulfed by the reticuloendothelial system, thanks to their unique surface polysaccharides and protein (CD47) structure. The limited cellular content and simpler genetic backgrounds of mature red blood cells facilitate membrane separation and extraction, thus promising considerable potential for red blood cell membrane biomimetic nanocarriers in tumor therapy. Furthermore, the fluidity of the phospholipid layer allows the red blood

cell surfaces to acquire tumor targeting specificity and functionalization. In 2011, Hu and his team proposed a new method to fabricate red blood cell membrane biomimetic nano-delivery systems by co-extruding PLGA microspheres and red blood cell membranes using a top-down approach. This study demonstrated that the system preserved the functionality of the red blood cell membrane, achieving a half-life in circulation (t1/2) of 39.6 hours in nude mouse models, substantially outperforming traditional PEG-modified nanodrugs (15.8 hours). This approach provides an innovative path to enhance the biocompatibility of nanocarriers via biological membranes. Recently, researchers have integrated biomimetic red blood cell technology with photothermal therapy and immunotherapy to target malignant tumors. Yang and his colleagues designed a multifunctional nano-drug delivery system by employing thermally sensitive nitric oxide donors PAAV-SNO polymers modified with red blood cell membranes containing NIRII photothermal agents (IR1061) and IDO-1 inhibitor 1-methyltryptophan. Both in vivo and in vitro tests revealed that this nanodrug demonstrated a long circulation time, targeted accumulation at tumor sites in animals, controlled drug release under NIRII laser irradiation, induced immunogenic cell death (ICD) of tumor cells through local hyperthermia from photothermal therapy, and recruited CD8+ T lymphocytes at tumor sites. Furthermore, interference with IDO-1 activity through locally produced nitric oxide normalized tumor vessels while programming the tumor microenvironment (TME) to stimulate an immune response, thus achieving experimental treatment for primary and metastatic breast cancer. Traditionally, the primary technique for actively targeting nanomedicines has involved chemical surface modification, which may compromise the integrity of red blood cell membranes. To overcome this challenge, a lipid insertion technique has been developed to functionalize these membranes. In one such example, Fang et al. first attached folic acid (FA) to distearoyl phosphatidylethanolamine (DSPE) and then inserted it into the red blood cell membrane. Nanocarriers enveloped by these ligand-functionalized red blood cell membranes demonstrated active targeting ability in both in vitro and in vivo tumor models. In summary, biomimetic nanodrug delivery systems based on erythrocytes have addressed some limitations associated with traditional nanomedicines, such as poor biocompatibility and high immunogenicity. These systems could provide a framework for clinical drug translation; however, further development and translation face new challenges, including ensuring contamination-free storage of red blood cells and considerations for blood type matching when utilizing erythrocytes.

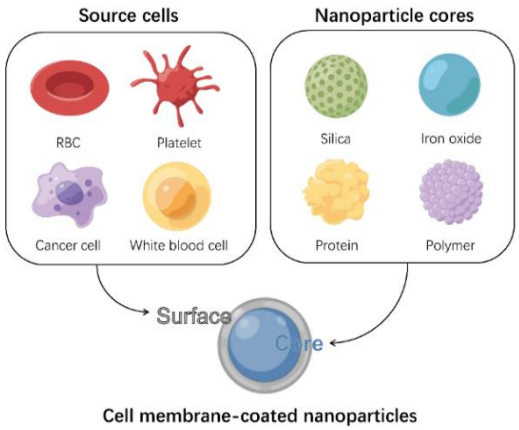

Figure 3. Cell membrane-coated nanoparticles. Various cell types have been developed as cell membrane sources for coating nanoparticles, each cell membrane type endowing nanoparticles with unique characteristics.

3.2. Immune cell membranes-coated nanoparticles

Chronic inflammation is a primary pathological feature of tumor growth. This process involves various inflammatory cells, such as neutrophils, macrophages, dendritic cells, eosinophils, basophils, NK cells, as well as T and B lymphocytes, which contribute to tumor progression. Concurrently, tumor cells overexpress various cytokines

and chemokines to attract a range of immune cells. Consequently, it is plausible to develop immune cell membrane biomimetic drug delivery systems to target anti-tumor drugs, utilizing the interaction between surface antigens and antibodies. Macrophages, immune cells capable of engulfing and destroying foreign substances, target the inflammatory environment of tumors and increase the binding of nanodrugs to tumor cells via specific surface antigens. In a study by Parodi et al., nanoporous silica particles were coated with macrophage membranes containing CD45, CD11c proteins, and multifunctional polysaccharide molecules29. This coating prolonged the in vivo circulation time of nanodrugs and their accumulation at the tumor site, by preventing rapid elimination. The study also found that macrophage membranes interacted with ICAM-1 receptors on tumor vascular endothelial cells to promote drug concentration at the tumor site. Furthermore, modification of biomimetic cell membranes can enhance carrier adhesion to tumor cells for targeted drug delivery, given the role of macrophages in cancer progression and metastasis. In vivo imaging of 4T1 breast cancer-bearing mice showed effective accumulation of liposomes, coated with macrophage membranes, in tumors after 48 hours, thereby inhibiting breast cancer lung metastasis. Neutrophils, a key type of white blood cells in mammals, can specifically interact with circulating tumor cells (CTCs) and direct them to tumor inflammation sites and bloodstream via adhesion factors such as LFA-1-ICAM-1, L-selectin-CD44, and β1 integrin VCAM-1. Their chemotactic properties inspired Kang et al. to coat PLGA with neutrophil membrane containing a central granule for targeting malignant melanoma. The study demonstrated significantly increased cytotoxicity in the B16F10 mouse melanoma cell line. Neutrophils have also been shown to penetrate the blood-brain barrier for glioma treatment. XUE et al. designed neutrophil membrane-modified paclitaxel liposome nanoparticles for postoperative glioblastoma recurrence prevention33. Following surgical resection of mouse glioblastoma, these biomimetic nanocarriers, constructed from neutrophils, were drawn to the tumor site by abundant inflammatory factors, where they released the loaded drugs to exert anti-tumor effects, showing excellent tumor inflammatory targeting capabilities. Other representative immune cells such as T and NK cell membranes have also been used in biomimetic nanocarrier systems preparation. T cells, essential lymphocytes involved in cellular immune responses, can target and destroy tumor cells, making them potentially useful in cancer treatment. Recently, a biomimetic drug delivery system known as TPNP, based on cytotoxic T cell membrane-loaded paclitaxel, was subjected to low-dose local radiation treatment. The cytotoxic T lymphocyte membrane effectively prolonged the in vivo circulation time of TPNP nanoparticles; post-radiation treatment, the induced T lymphocyte membrane-wrapped TPNP targeted the gastric cancer microenvironment, triggering paclitaxel release and synergistically inhibiting gastric cancer progression. T cell-mediated immunotherapy has also attracted significant attention in tumor treatment. NK cells are granular lymphocytes that protect hosts against cancer cells by recognizing abnormally expressed major histocompatibility complex class 1 (MHC-1) molecules. The incorporation of TPP into NK-MPEG-PLGANPs inhibited primary tumor cell proliferation via photodynamic therapy (PDT) while triggering immunogenic cell death (ICD) in dying tumor cells that activated antigen-presenting cells (APCs). Under near-infrared light irradiation, Ce6 experienced energy level transition to achieve photothermal/photodynamic synergistic therapy for tumors. Concurrently, NK cell membranes also have immunostimulatory functions, ultimately achieving experimental therapeutic effects on lung cancer.

3.3. Cancer cell membranes-coated nanoparticles

Tumor cells exhibit the potential for infinite proliferation and can be easily cultivated in vitro, providing a substantial supply of tumor cell membranes. These membranes can confer nanoparticles with immune evasion capabilities, extending their circulation time in the bloodstream. Additionally, tumor cell membranes retain homologous targeting and antigen library functions from their source cells, primarily due to membrane surface proteins such as N-cadherin protein, galectin-3, and epithelial cell adhesion molecule (EpCAM). This can be exploited for highly specific tumor-targeted therapy and immunotherapy. Research has demonstrated that HepG-2

tumor cell membrane-modified PLGA nanoparticles loaded with doxorubicin are taken up more effectively by homologous tumor cells compared to conventional nanoparticles. In xenograft mouse models carrying HepG2 in vivo, biomimetic PLGA nanodrugs demonstrate potent anti-tumor effects and low in vivo toxicity due to their extended blood circulation and immune evasion capabilities. Recently, stimulus-responsive tumor cell membrane biomimetic nanoparticles have gained increasing attention. These nanoparticles are designed to respond to the unique conditions of the tumor microenvironment. For example, Liu et al. reported a prostate cancer LNCaP-AI cell membrane-coated doxorubicin-loaded silica nanoparticle (Dox/MSN@CaCO3@CM) in which CaCO3 serves as a pH-responsive switch layer for controlled drug release39. Compared to free Dox, Dox/MSN@CaCO3@CM demonstrates efficient internalization into LNCaP-AI prostate cells. Under acidic pH conditions, the CaCO3 layer decomposes to release the loaded Dox, inducing high levels of cellular apoptosis. In vivo studies showed this nanodrug significantly inhibited tumor growth.The clinical success of immune checkpoint inhibition (ICI) and chimeric antigen receptor T-cell therapy (CAR-T) has highlighted the potential of cancer immunotherapy. By coating nanoparticles with cancer cell membranes, antigen proteins can be manipulated to perform various necessary immune functions, offering a novel method to enhance cancer immunotherapy. WANG et al. designed B16-OVA cancer cell membrane-coated nanoassemblies (OVANPs) loaded with photosensitizer (Ce6) and ovalbumin antigen (OVA). By spatially packaging the antigen OVA into a photosensitizer (Ce6) nanocarrier, the immunopotential of photodynamic therapy (PDT) was enhanced, triggering a cascade reaction for PDT-immunotherapy. Ce6-loaded OVANPs coated with B16-OVA cancer cell membrane demonstrated homologous tumor targeting in vivo. Laser irradiation significantly inhibited tumor growth, and B16-OVA-bearing mice did not exhibit notable side effects. Notably, a significant increase in CD+4T and CD+8T cells at the tumor site was observed, augmenting the photodynamic immunotherapy of the antigen nanocarrier. Furthermore, Kroll et al. constructed PLGA15NPs coated with B16-F10 cancer cell membranes and loaded the nucleic acid-based adjuvant CpG oligodeoxynucleotide 1826 (CpG) into the NP core to study its combined effect with an anti-CTLA4 and PD-1 checkpoint blockade mixture41. The NPs concurrently transported potent cancer antigens and adjuvants to promote antigen presentation. Interestingly, single checkpoint blockade or CpG-CCNPs cocktail alone did not inhibit the growth of the tumor in C57BL/6 mice, but their combination synergistically promoted a powerful anti-tumor response and immune modulation. In summary, delivering tumor antigens solely from cell membranes may not be enough to overcome the immunosuppressive tumor microenvironment. However, combining this strategy with immune checkpoint blockade therapy or different adjuvants may achieve optimal anti-cancer effects.

3.4. Hybrid cell membranes-coated nanoparticles

Recent studies have been focused on the development of hybrid membrane biomimetic nanocarriers, which involve combining cell membranes from different sources. This approach leverages the distinct properties of each cell membrane to enhance the overall characteristics of the nanocarriers. For example, DEHAINI et al. coated nanoparticles with a mixture of red blood cell and platelet membranes, resulting in double-membrane-coated nanoparticles. These nanoparticles exhibited exceptional circulation and distribution in a mouse model, demonstrating the advantages of cross-hybrid membrane features and good biocompatibility. Another study by Wang et al. involved the creation of a hybrid membrane using red blood cell and melanoma tumor cell membranes, which were modified by loading CuS nanoparticles containing docetaxel. This hybrid membrane, known as DCuS@[RBCB16] NPs, showed prolonged circulation in the bloodstream, targeted the tumor effectively, and achieved nearly 100% inhibition of melanoma tumor growth through a combination of chemotherapy and photothermal therapy. Furthermore, there have been advancements in developing other types of hybrid membrane mimetic nanoparticles, such as platelet-leukocyte hybrid membrane mimetic nanoparticles, red blood cell-macrophage hybrid membrane mimetic nanoparticles, and tumor stem-cell-platelet hybrid membrane mimetic

nanoparticles. These nanoparticles hold great promise for personalized treatment against various tumors. These findings provide valuable technical support for constructing multifunctional cellular biomimetic drug delivery platforms that can be customized to meet individual patient requirements.

3.5. Other cell membranes-coated nanoparticles

Stem cells are highly adaptable cells with low immunogenicity and the ability to self-renew. Extensive research has demonstrated that specific types of stem cells, including mesenchymal stem cells (MSCs), neural stem cells, and hematopoietic stem cells, possess the ability to target tumor cells and track infiltrating tumor cells. This is attributed to the presence of various receptors on their cell membranes, such as cytokine receptors (ILR1, ILR3, ILR4, TNFR, and IFNγR), growth factor receptors (TGF-β, HGF), extracellular matrix receptors (CD44, integrins), chemokine receptors (CXCR, CCR), and cell-cell interaction receptors (Notch, ICAM, and VAM1)45,46. By combining nanoparticles with stem cell therapy using MSC-membrane-coated nanoparticles (NPs), it becomes possible to replicate the multifunctional capabilities of stem cells while retaining the advantageous nano-scale drug-loading properties of NPs. Thus, MSC-membrane-coated NPs exhibit significant potential for anti-tumor treatments due to their inherent anti-tumor properties and inflammatory migration abilities. The Mu research group employed a low-permeation processing technique to extract mesenchymal stem cell membranes, which were then used to encapsulate iron oxide nanoparticles carrying siRNA for photothermal/gene synergistic therapy against tumors47. Experimental results revealed that these nanodrugs could selectively deliver siRNA to subcutaneously transplanted tumor sites in mice and induce apoptosis in cancer cells. When combined with photothermal therapy using iron oxide nanoparticles, the nanodrugs exhibited notable anti-tumor effects. Exosomes are small membrane vesicles, ranging from 30 to 120 nm in size, that are released by various cell types. They possess the ability to transport bioactive substances, such as proteins, to target cells and trigger cellular responses. Furthermore, exosomes have low immunogenicity and high loading capacity, making them promising candidates for cancer therapy48. Studies have demonstrated that exosomes exhibit superior biological utilization and fewer adverse reactions compared to artificial chemical delivery carriers, owing to their composition of lipids, proteins, and other natural components. Exosomes can be efficiently internalized by target cells with minimal immune clearance, demonstrating good tolerance even after repeated injections. Yong et al. developed a biocompatible tumor cell-derived exosome-mimetic porous silicon nanoparticle (PSiNP) for targeted delivery of doxorubicin (Dox) in cancer therapy49. The Dox-loaded PSiNPs coated with exosomal membranes (DOX@E-PSiNPs) were generated through the endocytosis of DOX@E-PSiNPs by tumor cells, followed by their extracellular release via exocytosis. In subcutaneous, orthotopic, and metastatic mouse models of tumors, DOX@E-PSiNPs exhibited enhanced accumulation in tumors and extravasation from blood vessels into the deeper regions of tumors, resulting in significant antitumor effects. While extracellular vesicles, including exosomes, represent a unique type of nanocarrier with potential applications in tumor diagnosis and treatment, there are challenges to overcome, such as achieving high loading capacity and facilitating clinical translation. Further research is required to improve our understanding of surface modification, purification methods, and the mechanisms of action of extracellular vesicles to enhance their safety evaluation before their widespread clinical utilization can be realized.

4. Cell membranes-coated nanoparticles in cancer therapy

4.1. CMNP in cancer imaging

Cell membrane-coated nanoparticles have emerged as versatile platforms not only for drug delivery in cancer therapy but also for various biomedical imaging modalities such as magnetic resonance imaging (MRI), computed

tomography (CT), and fluorescence imaging. Fe3O4 nanoparticles, a novel nanomaterial with low systemic toxicity, excellent stability, and biocompatibility, can serve as effective MRI contrast agents. The incorporation of cell membranes onto Fe3O4 nanoparticles significantly enhances their delivery efficiency. In a study by Rao et al., red blood cell membrane-coated Fe3O4 nanoparticles (Fe3O4@RBC-NP) were developed, demonstrating great potential for MRI and drug delivery applications. Additionally, due to the photothermal conversion capabilities of superparamagnetic iron oxide, these nanoparticles can be employed in magnetic hyperthermia therapy. Fluorescence imaging represents a highly effective strategy for tumor imaging in both biological research and clinical applications. To this end, researchers have developed cancer cell membrane-coated upconversion nanoparticles (CC-UCNP) that exhibit prolonged blood circulation time, immune evasion, and homotypic tumor targeting capabilities. CC-UCNP can convert near-infrared fluorescence to visible light for in vivo tumor imaging, showcasing their potential for cancer diagnosis and treatment. Moreover, cell membrane-based delivery systems enable the integration of fluorescence imaging with other therapeutic strategies. For instance, Chen et al. reported a cancer cell membrane biomimetic nanoparticle loaded with indocyanine green (ICNP), which allows high-resolution real-time tumor monitoring and effective tumor treatment through fluorescence and photoacoustic dual-mode imaging and photothermal therapy (PTT).

In summary, the combination of cell membranes with nanoparticles offers promising opportunities in biomedical imaging, including MRI, CT, and fluorescence imaging. Fe3O4 nanoparticles coated with cell membranes enhance MRI contrast, while cancer cell membrane-coated nanoparticles enable targeted and efficient fluorescence imaging for cancer diagnosis and treatment. These advancements demonstrate the potential of cell membrane-based delivery systems in integrating imaging and therapeutic modalities for improved biomedical applications.

4.2. CMNP in phototherapy for cancer

Phototherapy, a non-invasive cancer treatment strategy, utilizes laser irradiation to selectively target and treat tumors, encompassing two main approaches: photothermal therapy (PTT) and photodynamic therapy (PDT)55. PTT is a minimally invasive treatment method with low systemic toxicity that employs photosensitizers to achieve thermal ablation. Nanoparticle-based drug delivery systems (DDS) have shown promise in enhancing the bioavailability of water-insoluble drugs and improving the accumulation of therapeutic agents at tumor sites. Cell membrane-coated nanoparticles have emerged as a valuable tool to enhance the delivery efficiency of photosensitizers for PTT. Meng et al. developed macrophage membrane-wrapped magnetic iron oxide nanoparticles (Fe3O4@MM NP) that exhibited excellent biocompatibility, prolonged circulation time, superior tumor targeting, and efficient PTT effects against breast cancer in vivo56. PDT is a cancer treatment strategy that induces cell death in tumors by generating singlet oxygen through the activation of photosensitizers with specific wavelength light57. In recent studies, various cell membrane types, such as red blood cell membranes (RBM)58, platelet membranes, stem cell membranes59, and cancer cell membranes (CCM)60, have been coated onto nanoparticle surfaces to deliver anti-tumor PDT agents. Ding et al. developed RBM-coated upconversion nanoparticles (UCNP) modified with folic acid (FA) and triphenyl phosphonic acid (TPP) as targeting moieties, which effectively generated singlet oxygen under 980 nm irradiation. Due to the unique oxygen-carrying properties of red blood cells, these RBM-coated nanoparticles demonstrated superior singlet oxygen penetration compared to free PDT agents and other cell membrane-coated nanoparticles. Furthermore, the combination of RBM with targeting molecules significantly enhanced the efficiency of PDT tumor treatment using these nanoparticles58. CCM, with its homotypic targeting capabilities, has also garnered significant attention. Yang reported CCM-coated silica nanoparticles loaded with chlorin e6 (Ce6) (CM/SLN/Ce6) that exhibited excellent stability and homotypic targeting properties, making them promising targeted PDT agents for tumor treatment61.

In summary, phototherapy encompasses PTT and PDT as effective and non-invasive strategies for cancer

treatment. Cell membrane-coated nanoparticles, including macrophage membrane-coated nanoparticles for PTT and various cell membrane types for PDT, have demonstrated improved delivery efficiency of photosensitizers and enhanced therapeutic outcomes. These advancements hold great potential for the development of targeted and efficient cancer treatment strategies.

4.3. CMNP in cancer chemotherapy

Chemotherapy is a conventional cancer treatment method widely used in clinical settings. However, its effectiveness is limited by strong systemic toxicity and low bioavailability of chemotherapeutic drugs. Hydrophobic nature of many drugs further contributes to poor drug absorption and bioavailability. Overcoming these challenges requires the development of novel chemotherapeutic drugs and exploring new formulations for existing drugs62,63. Nanomaterials have emerged as promising drug delivery systems (DDS) for chemotherapy. Numerous studies have shown that nanoparticle-based DDS can enhance the therapeutic effects of chemotherapeutic drugs. To further improve the biocompatibility, targeting, and circulation time of drug-loaded nanoparticles, researchers have employed cell membranes to create biomimetic nanoparticles. Cancer cell membranes (CCM) confer immune evasion and homotypic targeting capabilities to nanoparticles when coated on their surfaces. Xu et al. reported the preparation of CCM-coated poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with doxorubicin (DOX) using CCM derived from HepG2 hepatocellular carcinoma cells. The resulting CCM-coated PLGA-DOX nanoparticles, with a diameter of approximately 100 nm and a zeta potential of approximately -29.49 mV, exhibited homotypic targeting, enhancing the uptake of DOX by HepG2 cells in vitro. Compared to free DOX, these biomimetic nanoparticles demonstrated extended circulation time, immune evasion, and tumor targeting effects, leading to potent antitumor efficacy and reduced systemic toxicity in HepG2 xenograft mouse models64. Blood cells, including red blood cells (RBCs), white blood cells, and platelets, can also serve as sources of cell membranes for coating nanoparticles to improve the delivery efficiency of chemotherapeutic drugs. Zhang et al. reported RBC membrane (RBM)-coated poly lactide (PLA) nanoparticles loaded with DOX. Two different methods were employed: physical encapsulation and chemical conjugation. The study demonstrated that chemical conjugation resulted in nanoparticles with higher drug loading and improved stability. Furthermore, RBM-coated nanoparticles exhibited superior therapeutic effects against acute myeloid leukemia compared to free DOX65.

In conclusion, the use of cell membrane-coated nanoparticles holds promise for enhancing the delivery efficiency and therapeutic efficacy of chemotherapeutic drugs. Cancer cell membranes and blood cell membranes have been successfully utilized to create biomimetic nanoparticles, offering improved targeting, prolonged circulation, and reduced systemic toxicity. These advancements provide potential solutions for improving chemotherapy outcomes and mitigating associated side effects.

4.4. CMNP in cancer immunotherapy

Cancer immunotherapy is a promising treatment approach that harnesses the immune system to inhibit tumor progression and induce anti-tumor immune responses66. However, challenges remain in developing immunotherapies with controllable immune system regulation, low systemic toxicity, and high anti-tumor efficiency while minimizing non-specific inflammation and other serious side effects67. Enhancing the therapeutic effects of cancer immunotherapy drugs while reducing systemic side effects is crucial for achieving more effective treatments. Nanoparticle-based drug delivery systems (DDS) offer potential solutions by protecting immune-related components during circulation, efficiently delivering tumor-associated antigens (TAA) and adjuvants, and enabling environment-responsive drug release to enhance immunotherapy effects and reduce systemic toxicity68. Various cell membranes can be used to coat nanoparticles, improving the delivery of TAAs and adjuvants. For instance, Lang

et al. mixed platelet and white blood cell membranes, coated them on immunomagnetic beads, and functionalized them with anti-EpCAM to create hybrid nanoparticles (HM-IMB)69. These hybrid nanoparticles exhibited enhanced tumor cell binding ability, reduced uptake by white blood cells, and effective separation of tumor cells in circulation. Neutrophil membrane-coated PLGA nanoparticles (NM NP) have also been developed, showing efficient identification of circulating tumor cells (CTCs) in vivo. Carfilzomib-loaded NM NP were able to eliminate CTCs in circulation and prevent early tumor cell metastasis70. Moreover, cell membrane-based coatings, such as cancer cell membranes (CCM), can not only improve the transport efficiency of drugs but also serve as a source of TAAs and be incorporated into cancer vaccines. Yang et al. developed a CCM-coated PLGA nanoparticle loaded with imiquimod (R837) and further modified with mannose (MAN). This nano-vaccine efficiently facilitated antigen-presenting cells (APCs) recognition and internalization, inducing an effective anti-tumor immune response. When used as a therapeutic immune agent, the nano-vaccine combined with immune checkpoint inhibitors showed promising tumor treatment effects71. Nanoparticle-based DDS enable the combination of immunotherapy with other treatment modalities such as photothermal therapy (PTT) or chemotherapy, leading to synergistic cancer treatments. PTT can induce the production of TAAs, triggering anti-tumor immune responses. When combined with nanoparticle-based immunotherapy, the vaccine-like effect of photothermal agents can inhibit the growth of residual tumor cells and suppress tumor cell metastasis68. For example, Liang et al. designed a biomimetic formulation using black phosphorus quantum dots (BPQD). Near-infrared (NIR) irradiation can stimulate the photothermal effect of the formulation, ablating tumor tissue and generating TAAs to induce anti-tumor immune responses, thereby further suppressing tumor development, metastasis, and recurrence. Coating red blood cell membranes (RBM) onto BPQD surfaces prolonged nanoparticle circulation time and promoted tumor site accumulation. Additionally, combining BPQD-RMNV with PD-1 antibodies enhanced anti-tumor immune responses for immunotherapy72. Chemotherapy-based immunotherapy has also emerged as an effective cancer treatment method. Low-dose chemotherapy drugs can induce immunogenic cell death (ICD) in tumor cells, releasing TAAs. When used concurrently with immunomodulators, this can enhance TAA antigen presentation and induce tumor-specific immune responses. Therefore, combining chemotherapy and immunotherapy using nanoparticle-based DDS represents an effective cancer treatment strategy73.

4.5. CMNP in cancer vaccines

Cancer vaccines represent a promising approach in immunotherapy, as they induce tumor-specific immune responses and hold great potential74. However, challenges include the systemic toxicity of adjuvants and the low immunogenicity of tumor antigens. An ideal cancer vaccine should effectively activate the immune system, elicit potent tumor-specific immune responses, and have minimal side effects. Antigen-presenting cells (APCs), such as dendritic cells (DCs), play a crucial role in this process by capturing tumor-associated antigens (TAAs) along with adjuvants that stimulate DCs. Once activated, DCs present TAAs to T lymphocytes, leading to the activation of cytotoxic T lymphocytes (CTLs), helper T cells, and the production of antibodies to induce humoral immunity76,77. Furthermore, DCs can secrete IFN-α to activate natural killer (NK) cells, which contribute to anti-tumor immune responses. Overcoming the immunosuppressive tumor microenvironment is essential for the destruction of tumors by CTLs and NK cells (Figure 4). The systemic toxicity of cancer vaccines must be carefully controlled during this anti-tumor immune process78. To develop safe and effective cancer vaccines, several factors need to be considered. Adequate stimulation of APCs, particularly DCs, is crucial to avoid T cell tolerance and promote anti-tumor immune responses79. Improving the anti-tumor immune activation efficiency of the two fundamental components, TAAs and adjuvants, is essential. TAAs should possess tumor specificity to ensure the induction of tumor-specific immune responses while reducing systemic immunotoxicity. Immunostimulatory adjuvants and efficient drug delivery systems play key roles in enhancing the immune activation efficiency of cancer vaccines80. Cancer cell membranes

(CCM) serve as an important source of TAAs and can be coated on the surface of nanoparticles to improve drug delivery efficiency. Previous studies have demonstrated the strong anti-tumor effects of tumor vaccines based on CCM. For example, Kroll et al. developed PLGA nanoparticles coated with CCM loaded with CpG, resulting in a nanoparticle-based tumor vaccine that enhanced antigen presentation efficiency and activated downstream immune processes. When combined with immune checkpoint inhibitors, this tumor vaccine exhibited potent therapeutic efficacy81. Furthermore, researchers can introduce additional functionalities into CCM-based tumor vaccines through biological approaches. Co-loading high levels of TAAs and immunostimulatory adjuvants has proven effective in enhancing the efficacy of CCM-based tumor vaccines. Jiang et al. developed CCM-coated nanoparticles using B16-F10 mouse melanoma cells that were genetically modified to express OVA and the co-stimulatory marker CD80 prior to CCM extraction. The resulting engineered CCM-coated nanoparticles could directly stimulate T cells without the need for APCs, thereby achieving effective tumor immunotherapy82.

Collectively, cancer vaccines have the potential to induce tumor-specific immune responses. Improving the efficiency of immune activation requires careful consideration of factors such as TAAs, adjuvants, and drug delivery systems. Coating nanoparticles with CCM offers a valuable strategy for enhancing drug delivery efficiency and promoting anti-tumor immune responses. The development of safe and effective cancer vaccines is essential for advancing immunotherapy and improving cancer treatment outcomes.

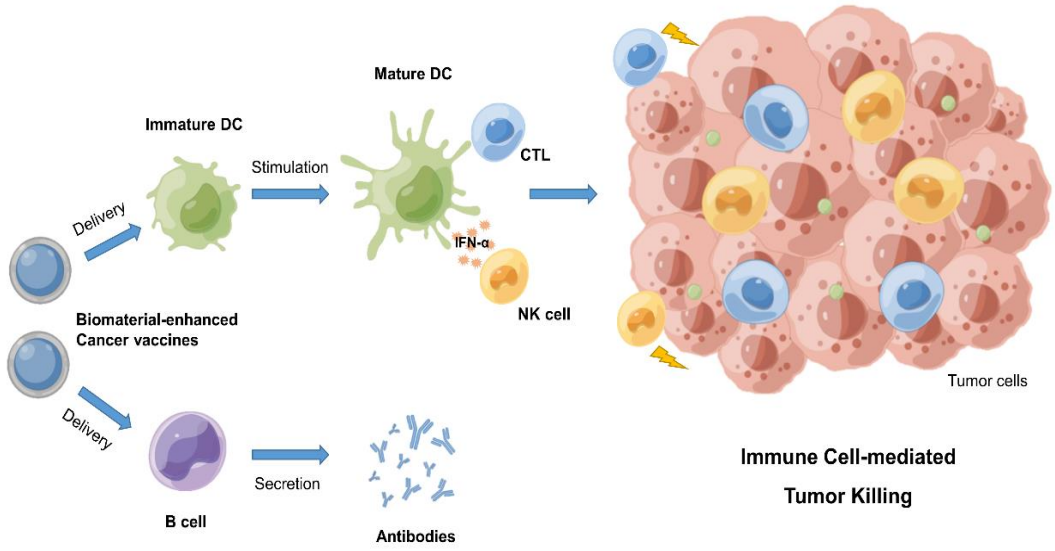

Figure 4. Schematic representation of antitumor immune responses induced by tumor vaccines based on biological nanomaterials.

5. Conclusion

This article explores the recent advancements in biomimetic nanocarrier systems for tumor therapy, focusing on the utilization of cell membranes. These membranes offer a range of biological functions to nanocarriers without the need for complex synthesis designs. Compared to other drug delivery systems, membrane coating with cell membranes reduces immunogenicity and avoids clearance by the reticuloendothelial system, resulting in prolonged circulation time in the bloodstream. Moreover, biomimetic nanodrugs coated with macrophage, stem cell, or cancer cell membranes retain their inherent homing ability towards tumors and can overcome physiological barriers for active targeting and penetration into tumor sites. This has significant implications for the treatment of primary and metastatic tumors. The innovative membrane coating technology enables the flexible fusion of different nanomaterials with various cell membranes, opening up broad application prospects in targeted drug delivery,

tumor therapy, and immune regulation. However, cell membrane biomimetic nanocarrier systems are still in their early stages and face challenges in transitioning to clinical trials. The methods for extracting and purifying cells are not yet fully developed, particularly for cells with short lifespans, which makes large-scale membrane extraction difficult. Additionally, identifying crucial proteins on the cell membrane while eliminating unwanted ones according to acceptable standards is complex due to the diverse array of proteins present. Current characterization methods for biomimetic nanoparticles have limitations, with successful encapsulation verified only through particle size detection and morphological observation. Protein imprinting analysis can confirm surface composition similarity but cannot ascertain the potential partial destruction of the cell membrane after encapsulation. Furthermore, most studies have been conducted on mouse models, necessitating the evaluation of immunogenicity in humans before clinical implementation. To overcome these challenges and establish safe and effective controllable strategies for large-scale industrial production and quality control of cell membrane biomimetic nanodrugs, innovative research and development in bionic nanotechnology is imperative.

Conflict of interest

All the authors claim that the manuscript is completely original. The authors also declare no conflict of interest.

Author contributions

Conceptualization: Yasir Hameed, Yuan Gu; Investigation: Yasir Hameed, Mohsen Nabi-Afjadi; Methodology: Yasir Hameed; Writing–original draft: Yasir Hameed; Writing–review & editing: Yasir Hameed, Mohsen Nabi-Afjadi.

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